Remarks

In the final Office Action dated April 5, 2001, the Examiner rejected claims 1-18 under 35 U.S.C. § 102(b) as being anticipated by *Shalon*, et al. (Genome Research, July 1996, hereinafter "*Shalon*") and maintained the rejection earlier made in the rejection of October 12, 2000. In response, the claims have been amended to clarify the Examiner's understanding of Applicants' argument on pages 4 and 5 filed January 16, 2001 and to correct a typographical error in the recitation of "image" in claim 10, to now correctly recite "imager."

Applicants contend that this amendment together with the following clarifications is believed to be fully responsive to the Examiner's office actions of October 12, 2000 and April 5, 2001, and to place this application in condition for allowance, which allowance is respectfully requested.

Applicants' invention provides a method and system for creating crosstalk corrected data of microarray substrates experiencing crosstalk caused by overlapping dye emission spectra with correction factors that are based on calibration spots from the microarray substrates.

The Examiner states that Applicants' arguments heretofore with respect to *Shalon* (page 4 and 5 of previously filed reply of January 16, 2001) are not understood. Applicants seek to clarify their argument with the remarks below.

On page 644, *Shalon* refers to "optical crosstalk," specifically that "the red green hybridization were corrected for optical crosstalk, between the fluorescein and lissamine channels, using experimentally determined coefficients." There are at least two significant differences between *Shalon's* single reference to crosstalk, and crosstalk correction, and the method and system described and claimed by Applicants.

Firstly, *Shalon's* scanning apparatus, at page 644, utilizes "simultaneous specimen illumination at 488.0 nm and 568.2 nm. ... An epifluorescene configuration with dual-band 488/568 primary beamsplitter (Chroma) excited both fluorophores simultaneously and directed fluorescence emissions toward a two-channel detector." Simultaneous excitation of multiple fluorophores, as opposed to the sequential excitation recited by Applicants, creates a purely optical mechanism for crosstalk that does not exist in the sequential-scanning embodiments claimed by Applicants and recited in the specification at page 1, line 22. Detectors used in *Shalon's* scanning devices respond equally well to reflected excitation light as they do to emitted fluorescence light which has a wavelength a few nanometers longer. Extensive effort is put into the *Shalon* type scanning system to define, manufacture, and install optical filters that maximize the detector's efficiency at receiving the fluorescence wavelength bands while also maximally blocking or rejecting the excitation wavelength bands. Also, the additional complication of multiplexing multiple wavelengths simultaneously limits the performance of *Shalon's* filtering elements. The two-color scanner of *Shalon* which simultaneously excites multiple wavelengths will generate purely optical crosstalk caused by the detection in detector B of reflected excitation light from channel A. As such, *Shalon* does not refer to correcting crosstalk caused by overlapping emission spectra as also claimed by Applicants.

Secondly, *Shalon* refers to correction "using experimentally determined coefficients," but makes no mention of a method or system to generate and determine the coefficients, let alone any means to apply these coefficients automatically from control spots on his array, as claimed by Applicants.

As such, and since *Shalon* fails to teach the above-identified claim limitations, *Shalon* cannot teach each element of Applicants claimed invention. Therefore, Applicants respectfully contend the rejection of claims 1-18 under 35 U.S.C. § 102(b) over *Shalon* has been over come, and the these claims are thus in proper condition for allowance of the present application.

Furthermore, the Examiner asserts that U.S. Patent No. 5,807,522 to Brown et al. (hereinafter "*Brown*") teaches that the optical crosstalk referred to by *Shalon* is caused by overlapping dye emission spectra. Applicants respectfully contend that it is improper to combine *Brown* with the teachings of *Shalon* under a 35 U.S.C. § 102(b) rejection, and, that even if such a combination were possible, this Action cannot then properly carry the designation of being final as the introduction of *Brown* would initiate a new grounds for rejection. MPEP § 2131.01 recites that secondary references may be used in 35 U.S.C. § 102 rejections to enable a disclosure, explain terms and phrases, or show inherent characteristics. Specifically, "extrinsic evidence [from a secondary reference] may be used to explain but not expand the meaning of terms and phrases used in the [primary] reference relied upon as anticipatory of the claimed subject matter." (*In Re Baxter Travenol Labs.*, 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991) (modifications added)) As discussed above, *Shalon* makes no reference to crosstalk caused by overlapping dye emission spectra, in fact the system of *Shalon* teaches away from such a suggestion, thus it can only be concluded that the Examiner is using *Brown* to expand the teachings of *Shalon*. The Examiner's action is improper for a 35 U.S.C. § 102(b) rejection.

Moreover, even if these references were combined, Applicants assert that such a combination would also fail to particularly teach each element of Applicants claimed invention. Simply, regardless of whether or not either reference teaches to optical crosstalk caused by overlapping dye emission spectra, neither reference discloses Applicants's means for "sequentially generating a dye image containing at least one of the calibration dye spots for each of a plurality of output channels" and "computing a set of correction factors from the optical measurements" for "applying the set of correction factors to data obtained from the sequentially generated microarray images," as claimed by Applicants. *Brown*, like *Shalon*, only merely states that optical crosstalk between the fluorophores are corrected. Clearly, this cannot teach the above-identified steps claimed by Applicants.

Applicants respectfully contend that their method and system for creating crosstalk corrected data of microarray substrates experiencing crosstalk caused by overlapping dye emission spectra with correction factors that are based on calibration spots from the

microarray substrates, recites limitations and teachings which are significantly different than anything taught or suggested by *Shalon*. As such, Applicants respectfully contend that their application is thus in condition for allowance, which allowance is respectfully requested.

Consequently, and in view of the above remarks, Applicants respectfully contend that each of the Examiner's rejections have been fully replied to and invention clarified, and that the application is in condition for allowance, which allowance is respectfully requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A method for automatically creating crosstalk-corrected data of a microarray wherein crosstalk is caused by overlapping dye emission spectra, the method comprising:

providing a microarray substrate having calibration dye spots, each of the calibration dye spots comprising a single pure dye;

for each of the calibration dye spots, sequentially generating a dye image containing at least one of the calibration dye spots for each of a plurality of output channels;

for each of the calibration dye spots, measuring an output of each of the output channels to obtain output measurements;

computing a set of correction factors from the output measurements; and

applying the set of correction factors to data obtained from the sequentially generated microarray images containing spots having dyes with excitation or emission spectra to obtain crosstalk-corrected data.

10. (Twice Amended) A system for automatically creating crosstalk-corrected data of a microarray wherein crosstalk is caused by overlapping dye emission spectra, the system comprising:

a microarray substrate having calibration dye spots, each of the calibration dye spots comprising a single pure dye;

an [image] imager having a plurality of output channels wherein for each of the calibration dye spots the [image] imager sequentially generates a dye image containing at least one of the calibration dye spots for each of the output channels;

means for measuring an output of each of the output channels for each of the calibration dye spots to obtain output measurements;

means for computing a set of correction factors from the output measurements; and

means for applying the set of correction factors to data obtained from the sequentially generated microarray images containing spots having dyes with excitation or emission spectra to obtain crosstalk-corrected data.